[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT, UNIVERSITY OF MICHIGAN]

THE ISOMERIC 4-AZABICYCLO[5.3.0]DECANES AND BIS-1,2-(β-AMINOETHYL)CYCLOPENTANES

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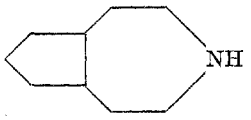
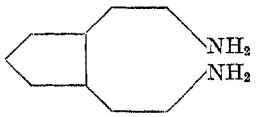
In connection with a study of substituted hexamethylenimines and other azepine derivatives, the two isomeric 4-azabicyclo[5.3.0]decanes (I) have been synthesized.



I



II

It was desired to compare the ease of closure of the seven membered ring with the parallel case [Ruggli (1), et al.] in which a similar ring is constructed on the *ortho* positions of benzene. In addition, the compounds (I) are of interest because of their relation to a heterocyclic azulene analog.

The two bicyclic isomers were obtained by the reductive cyclization, respectively, of the *cis*- and *trans*-cyclopentane-1,2-diacetonitriles with hydrogen at 120 atmospheres and 115° on Raney nickel. The conditions followed the experience of Ruggli (1), *et al.* in reducing *o*-phenylenediacetonitrile to 1,2,4,5-tetrahydro-3-benzazepine. The yields were not high and somewhat larger amounts of the diprimary amines (II) were obtained at the same time. A limited direct comparison of the reduction of the cyclopentane derivatives with Ruggli's synthesis showed slightly higher yields in the cyclopentane series. Yields reported by Ruggli, however, were still higher. The results suggest that the preparation of compounds (I) might be developed by detailed study to a fairly high level of efficiency. There was no significant difference between the yields of the *cis*- and *trans*-compounds.

The *cis*-cyclopentane-1,2-diacetonitrile and small amounts of the *trans*-isomer were synthesized by commonly used reactions from the corresponding cyclopentane-1,2-diacetic acids. The acids were obtained as a solid solution from ethyl adipate by the method of Linstead and Meade (2) and were separated according to the directions of Barrett and Linstead (3). In future preparations of the bicyclo compounds (I) it will probably be profitable to omit this rather laborious separation, since the picrates of the final products are much more readily separable.

A better supply of the *trans*-cyclopentane-1,2-diacetonitrile was obtained from *trans*-cyclopentane-1,2-dicarboxylic acid by the following reactions:

$$C_5H_8(COOH)_2 \xrightarrow{LiAlH_4} C_5H_8(CH_2OH)_2 \xrightarrow{SOCl_2} C_5H_8(CH_2Cl)_2$$

$$\xrightarrow{NaI} C_5H_8(CH_2I)_2 \xrightarrow{NaCN} C_5H_8(CH_2CN)_2$$

Inactivity of the dichloride to sodium cyanide led to the intermediate preparation of the iodide.

As might be expected, the boiling points of the 4-azabicyclo[5.3.0]decanes (*cis*, 93–95°/20 mm.; *trans*, 94–101°/23 mm.) are not different enough to distinguish them. Their individuality, however, is evident from their conversion to picrates which melt 20° apart and exhibit a depressed mixture melting point.

cis-4-Azabicyclo[5.3.0]decane survived exposure to severe dehydrogenation conditions (40% Pd-asbestos at 400°) without appreciable change and with corresponding negligible hydrogen production. Most of the starting amine was recovered as the picrate. After the attempted dehydrogenation, the same batch of catalyst supported the dehydrogenation of piperidine at a reasonable rate at 250°.

In justifying the assignment of structure I, it is first necessary to show the presence of the secondary amino group. To this end, the observation that the *p*-toluenesulfonyl derivatives are completely insoluble in strong NaOH is good but not entirely convincing evidence. The *cis*-isomer, however, shows the same reluctance as piperidine and 1,2,4,5-tetrahydro-3-benzazepine to react with nitrous acid, but does react slowly at steam-bath temperatures to produce an oil which is not soluble in aqueous hydrochloric acid. It is clear that the *cis*-compound is a secondary amine and highly probable that the *trans*-compound can be similarly classified.

The possibility of producing a piperidine or pyrrolidine derivative instead of structure I appears to be remote. Nitrile hydrogenations, in general, are not accompanied by isomerization to any appreciable extent. Consequently, there is little chance that such changes can occur either before or after cyclization.

The simplicity of the product mixture argues against isomerization after cyclization. Two products are separated by distillation, constituting the first and last of three fractions and accounting for about 70% of the material. Since both substances must be present in considerable amounts in the intermediate fraction, it is permissible to assume that the conversion to cyclic secondary amine and diprimary amine is of the order of 80% or higher. In this respect the reactions are closely similar to the reduction of *o*-phenylenediacetonitrile, where the secondary amine is demonstrably a hexamethylenimine derivative.

This indicates that the hexamethylenimine ring is essentially immune to contraction under the conditions of the hydrogenation. Models suggest that if ring strain contributes to susceptibility, isomerization should be more probable with the benzene derivative than with the substituted cyclopentanes.

Isomerization would probably have to start with the acquisition of a hydrogen atom at a point which could easily approach the surface. This would produce a potential free radical which might stabilize itself by an internal shift which expelled a hydrogen atom at some second point. There appears to be no good reason why this type of reaction should be limited to a single product. It would be expected, instead, to produce a relatively complex product mixture which could include primary and tertiary amines. In addition to isomerization, ring opening by hydrogenolysis would be very likely to occur at the same time, with further complication of the product mixture.

If the *cis*-compound were attacked at the bridgehead, the principal product might be *cis*-decahydroisoquinoline although nonamethylenimine and β-cyclopentyldiethylamine would also be probable by hydrogenolysis. The present *cis*-compound, as shown by the melting point of the hydrochloride (271°), is definitely different from either of the decahydroisoquinolines obtained by Witkop (4), whose hydrochlorides melted at 188° (*cis*) and 224° (*trans*). The possibility that the present *trans*-compound could be isomerized to a decahydroisoquinoline is too remote to require consideration. It is of some interest that the *cis*-picrate (I) melts 20° above the *trans*-picrate, while with Witkop's decahydroisoquinoline picrates the reverse relation between the *cis*- and *trans*-compounds occurs. The *cis*-decahydroisoquinoline picrate and the *trans*-4-azabicyclo[5.3.0]decane picrate have the same melting point (150°).

The failure of the *cis*-compound to evolve hydrogen under severe dehydrogenation conditions is a further argument against the presence of the pyrrolidine or piperidine ring, particularly the latter. The *cis*-compound would be expected to dehydrogenate more readily than the *trans* derivative and would be unlikely to resist dehydrogenation so completely if the smaller ring were present.

EXPERIMENTAL

cis-Cyclopentane-1,2-diacetamide. A solution of 0.1 g. of pyridine in 23 ml. of thionyl chloride was added to 27 g. of *cis*-cyclopentane-1,2-diacetic acid. After standing for two days, excess thionyl chloride was removed at aspirator pressure and the mixture was heated briefly on the steam-bath. The crude acid chloride, diluted with acetone, was added slowly, with stirring, to 120 ml. of 28% aqueous ammonia cooled by an ice-salt mixture. After 30 minutes the solid product was filtered off and recrystallized from water. Yield of diamide, 20 g. (75%), m.p. 249–250° dec.; very soluble in hot ethyl acetate or hot acetic acid, soluble in cold acetic acid or hot water, slightly soluble in hot ethanol or cold water.

Anal. Calc'd for $C_9H_{16}N_2O_2$: N, 15.21. Found: N, 15.26.

cis-Cyclopentane-1-acetamide-2-acetic acid was obtained from the acetone solution in the diamide preparation, by evaporation and acidification followed by several recrystallizations from water. Yield, 2 g., m.p. 200–201°.

Anal. Calc'd for $C_9H_{15}NO_3$: Neut. equiv., 185.2. Found: Neut. equiv., 184.1.

trans-Cyclopentane-1,2-diacetamide was prepared in precisely the same manner as the *cis*-isomer; m.p., 257–258° dec., mixture m.p. with the *cis*-compound, 241–243°.

Anal. Calc'd for $C_9H_{16}N_2O_2$: N, 15.21. Found: N, 15.25.

cis-Cyclopentane-1,2-diacetonitrile. A mixture of 6.5 g. of *cis*-cyclopentane-1,2-diacetamide, 5.4 g. of dried sodium chloride (5), and 3.8 ml. of phosphorus oxychloride was heated for 20 minutes at 110° under reflux in an oil-bath which could be lowered to control froth formation. The temperature was rapidly raised to 200° where it was held for five minutes, after which the product was distilled at 20 mm. with the bath temperature at 270°. The distillate, dissolved in ether, was washed with dilute sodium hydroxide, then washed with water, dried, and distilled. Yield, 85%, b.p., 116–118°/0.3 mm., n_D^{25} 1.4768, d_4^{25} 1.016.

Anal. Calc'd for $C_9H_{12}N_2$: N, 18.91. Found: N, 18.50.

trans-1,2-Bis(hydroxymethyl)cyclopentane. *trans*-Cyclopentane-1,2-dicarboxylic acid, m.p. 160–161°, was prepared according to Perkin (6) (low yield) and according to Fuson, *et al.* (7). The *trans*-di-acid, 6.8 g., was introduced by the Soxhlet extractor technique (8) into a stirred refluxing solution of 0.085 mole of lithium aluminum hydride in 200 ml. ether. After reaction, water was added, followed by 9 *M* sulfuric acid, and the aqueous layer was extracted five times with ether. From the combined ether extracts, by distillation after drying, there was obtained 4.4 g. of *trans*-1,2-bis(hydroxymethyl)cyclopentane, b.p., 117–118°/0.6 mm., n_D^{25} 1.4480.

Anal. Calc'd for $C_7H_{14}O_2$: C, 64.58; H, 10.84.
Found: C, 64.42; H, 11.07.

trans-1,2-Bis(chloromethyl)cyclopentane. Thionyl chloride, 4.7 ml., was added in 20 minutes, with stirring, to 6.8 g. of *trans*-1,2-bis-(hydroxymethyl)cyclopentane. The copious crystalline precipitate was loosened from the walls, stirring was continued for 90 minutes at room temperature, and the mixture was then heated for two hours on the steam-bath. The oil which separated with the addition of water was dissolved in carbon tetrachloride and the solution was washed successively with dil. sulfuric acid, conc'd sulfuric acid, and aqueous sodium bicarbonate. After drying, distillation yielded 6.7 g. of liquid, b.p. 96–96.5°/13 mm., n_D^{25} 1.4859, d_4^{25} 1.145.

Anal. Calc'd for $C_7H_{12}Cl_2$: C, 50.32; H, 7.24.
Found: C, 50.23; H, 7.24.

trans-Cyclopentane-1,2-diacetonitrile. trans-1,2-Bis(chloromethyl)cyclopentane, 9.1 g., was added to 17 g. of sodium iodide in 60 ml. of acetic acid and the mixture was heated, under nitrogen, for 20 hours near the boiling point. Addition of water precipitated an oil which was dissolved in ether and washed with sodium carbonate solution and with water. After drying, the solvent was removed under reduced pressure to leave the crude diiodide (17.9 g.) as a pale brown oil. This oil was added to 7.5 g. of sodium cyanide in 30 ml. of 60% aqeous ethanol and the mixture was refluxed for 22 hours. Water was added and ether and the ether extract was washed successively with dil. sodium hydroxide and dil. sulfuric acid. Fractional distillation of the dried ether solution yielded 5.2 g. of dinitrile, b.p. 109.5°/0.3 mm., n_D^{25} 1.4713, d_4^{25} 1.009.

Anal. Calc'd for $C_9H_{12}N_2$: N, 18.91. Found: N, 18.28.

cis-4-Azabicyclo[5.3.0]decane. cis-Cyclopentane-1,2-diacetonitrile (5.9 g.) in 50 ml. of abs. alcohol saturated with ammonia was shaken with 1.5 g. of W-2 Raney nickel and hydrogen at 120 atmos. The mixture attained a temperature of 115° in 35 minutes and was held at this temperature for one hour. Two such runs, combined, gave 3.3 g., b.p. 98–103°/23 mm.; 0.5 g. of an intermediate fraction; and 5.3 g., b.p. 142–144°/23 mm.

The lowest-boiling fraction, taken to be the cyclic secondary amine, was converted to the *picrate* (7.8 g.) which was recrystallized from ethanol, m.p. 169–170°.

Anal. (picrate) Calc'd for $C_{15}H_{20}N_4O_7$: C, 48.91; H, 5.47.
Found: C, 48.88; H, 5.56.

From the picrate was obtained the pure *secondary amine*, b.p. 93–95°/20 mm., n_D^{25} 1.4889, d_4^{25} 0.9330.

Anal. Calc'd for $C_9H_{17}N$: Neut. equiv., 139.24. Found: Neut. equiv., 139.2.

The *hydrochloride*, m.p. 270–271°, was recrystallized from ethanol.

Anal. Calc'd for $C_9H_{18}ClN$: Cl, 20.18. Found: Cl, 20.19.

The *N-(p-toluenesulfonyl)derivative* crystallized in flakes from a benzene-petroleum ether solution; m.p. 101–101.5°.

Anal. Calc'd for $C_{16}H_{23}NO_2S$: N, 4.77. Found: N, 4.50.

When a concentrated aqueous solution of the hydrochloride was treated with an equivalent quantity of sodium nitrite, a yellow oil, insoluble in acid, separated without significant gas evolution. When the free amine in dry ether was treated with carbon dioxide, a white solid, probably a carbamate, was rapidly formed. This solid was nearly insoluble in ether, ethanol, or water, but dissolved with gas evolution in dilute mineral acid.

cis-1,2-Bis(β-aminoethyl)cyclopentane. The highest-boiling fraction from the dinitrile hydrogenation was nearly pure *cis*-1,2-bis-(β-aminoethyl)cyclopentane.

Anal. Calc'd for $C_9H_{20}N_2$: Neut. equiv., 78.3. Found: Neut. equiv., 79.3.

The *dihydrochloride*, m.p. 216–217° was readily soluble in hot ethanol, slightly soluble in cold ethanol, and was recrystallized from ethanol and acetone.

Anal. Calc'd for $C_9H_{22}Cl_2N_2$: Cl, 30.94. Found: Cl, 30.82.

trans-4-Azabicyclo[5.3.0]decane was obtained by hydrogenating 4.5 g. of *trans*-cyclopentane-1,2-diacetonitrile under the conditions described above for the *cis*-isomer. From 3.6 g. of crude product, the lowest-boiling fraction, 1.0 g., b.p. 94–101°/23 mm., was treated with picric acid to give 2.3 g. of *trans-4-azabicyclo[5.3.0]decane picrate*, light yellow plates,

m.p. 150–151°. A mixture with the *cis*-picrate melted at 147–149°. The *trans*-picrate was more soluble in ethanol than the *cis*-isomer.

Anal. Calc'd for $C_{15}H_{20}N_4O_7$: C, 48.91; H, 5.47.
Found: C, 48.75; H, 5.50.

The *N-(p-toluene sulfonyl)derivative* crystallized in needles from petroleum ether, m.p. 72–72.5°, mixture m.p. with *cis*-isomer, 65–68°.

Anal. Calc'd for $C_{16}H_{23}NO_2S$: N, 4.77. Found: N, 4.94.

trans-1,2-Bis(β-aminoethyl)cyclopentane, b.p. 138–142°/23 mm., was converted to the *dihydrochloride*, which was recrystallized from aqueous ethanol.

Anal. Calc'd for $C_9H_{22}Cl_2N_2$: Cl, 30.94. Found: Cl, 30.87.

Attempted dehydrogenation of cis-4-azabicyclo[5.3.0]decane. Vapors of the secondary amine, 0.80 g., were passed over 40% Pd-asbestos in ten minutes at a bath temperature of 400°. Hydrogen evolution was negligible and no gaseous basic material was generated. The yellow liquid, 0.72 g., was diluted with dry ether and treated with carbon dioxide to precipitate a solid which was washed thoroughly with ether. More solid was obtained by concentrating the ether solution and again introducing carbon dioxide. The combined solid, with picric acid in boiling methanol, produced 1.60 g. of the picrate of the starting material, m.p. 169–170°.

Further manipulation of the ethereal residue gave 0.03 g. of a viscous orange colored oil of aliphatic amine odor. With picric acid in methanol a red oil formed which would not crystallize.

To test the catalyst, after completion of the attempted dehydrogenation, the bath temperature was lowered to 250° and 1.7 g. of piperidine was passed over the catalyst in two hours, to yield 23% of the theoretical volume of hydrogen for conversion to pyridine.

SUMMARY

The *cis*- and *trans*-cyclopentane-1,2-diacetonitriles have been synthesized and hydrogenated on Raney nickel at 115° and 120 atmospheres to produce the corresponding 4-azabicyclo[5.3.0]decanes and bis-1,2-(β-aminoethyl)cyclopentanes.

The picrates and N-(*p*-toluenesulfonyl)derivatives of the secondary amines and the hydrochlorides of both the primary and the secondary amines are described.

cis- and *trans*-Cyclopentane-1,2-diacetamide, *cis*- cyclopentane-1-acetamide-2-acetic acid, *trans*-1,2-bis-(hydroxymethyl)cyclopentane, and *trans*-1,2-bis-(chloromethyl)cyclopentane are described.

cis-4-Azabicyclo[5.3.0]decane is highly resistant to dehydrogenation.

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